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(54) Title: HYDROSOLUBLE ORGANIC SALTS OF CREATINE

(57) Abstract

Hydrosoluble organic salts of creatine are disclosed. The salts are useful in the dietetic and food industry.

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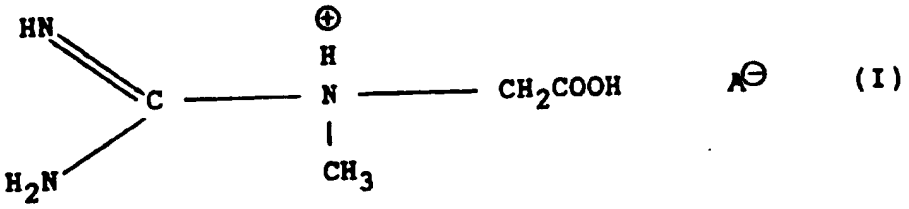
HYDROSOLUBLE ORGANIC SALTS OF CREATINE

The present invention refers to hydrosoluble organic salts of creatine of general formula I:



(I)

wherein $A^{\ominus}$ represents the anion of a mono, bi- or tricarboxylic acid. Preferred anions are the citrate, maleate, fumarate, tartrate or malate.

Creatine or N-(aminoiminomethyl)-N-methylglycine is a sarcosine derivative present in the muscle tissue of many vertebrates, man included, mainly combined with phosphoric acid in form of phosphorylcreatine and it is involved in the energy transfer from mitochondria to the ATP utilization sites.

Several studies indicate that there is a relationship between the creatine (phosphoryl creatine) concentration in the muscles having the function of keeping an high intracellular ATP/ADP ratio and maximum sustainable physical effort (Annu. Rev. Biochem. 54: 831-862, 1985; Science 24: 448-452, 1981; BESSMAN S.P., and F. SAVABI. The role of the phosphocreatine energy shuttle in exercise and muscle hypertrophy. In: Biochemistry of Exercise VII. A.W. Taylow, P.D. Gollnick, H.J. Gr en, C.D. Ianuzzo, E.G. Noble, G. Metivi r, and J.R. Sutton., Intl. Series Sports Scienc s 21: 167-178, 1990).

The creatine increase in diets may therefore be

useful to bring the plasma creatine concentrations at levels providing significant values of creatine itself in the muscle. The short creatine half-life in plasma (1-1.5 hours) makes however necessary to reach rapidly said levels and this, in view of the bioavailability degree of creatine, is obtainable only by the administration of high doses of 5-10 g (for mean body weights of 70 kg), amounts well tolerated because of the lack of toxicity of the compound.

The low solubility of creatine in water (1 g in 75 ml) is therefore a practical limitation to the possibility of marking immediately available in the specific diet the necessary amounts of creatine.

The present invention provides hydrosoluble stable organic salts of creatine of formula I characterized by high water solubility (from 3 to 15 times higher them that of creatine itself) and a process for their preparation. The salts of formula I are prepared by salifying creatine with the corresponding acids in aqueous or hydroalcoholic concentrated solution or in a water-immiscible solvent, at temperatures ranging from the room temperature to 50°C, optionally concentrating the solutions and filtering the crystallized salts. According to a preferred embodiment the salts of formula I are prepared by reacting creatine with an excess organic acid in ethyl acetate until the salt is completely formed, detectable with the IR analysis, cooling and filt ring. Th filtrated solvent, containing the excess acid is recycled and, after filling up of the components, is used for a further reaction.

The salts are characterized by IR, melting point, potentiometric and HPLC assay.

Table 1 reports the solubility of the salts I of the invention.

Table 1

Creatine salt	Water solubility % (g/100 ml)
Citrate	10
Maleate	19
Fumarate	3
Tartrate	8,5
Malate	4,5

Example 1

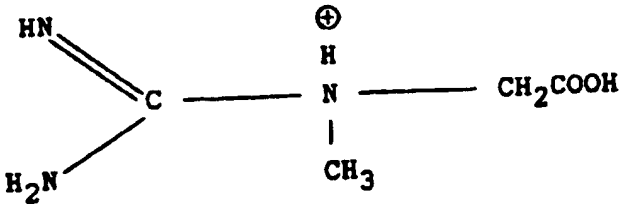
39.45 g (0.18 mol) of monohydrate citric acid are suspended in 100 ml of ethyl acetate. 20 g (0.134 mol) of monohydrate creatine are added to the stirred suspension at 20-25°C and the mixture is stirred 4 hours at 25°C. After IR control, the product is filtered and washed with ethyl acetate, then dried in oven at 50-55°C, obtaining 90% of salts, m.p. 112-114°C, 99.2% titer.

Example 2

14.9 g (0.1 mol) of monohydrate creatine are added to a solution of 11.6 g (0,1 mol) of maleic acid in 20 ml of water. The so obtained solution is concentrated, cooled to 5°C and the product filt red and dried und r vacuum at 50°C, obtaining 87% of salt, m.p. 128-129°C, 99.8% titer.

CLAIMS

1. Salts of creatine of general formula I:



(I)

wherein $A^{\ominus}$ represents the anion of a mono, bi- or tricarboxylic acid.

2. Creatine salts of claim 1 wherein $A^{\ominus}$ is the anion of citric acid.

3. Creatine salts of claim 1 wherein $A^{\ominus}$ is the anion of maleic acid.

4. Creatine salts of claim 1 wherein $A^{\ominus}$ is the anion of offumaric acid.

5. Creatine salts of claim 1 wherein $A^{\ominus}$ is the anion of tartaric acid.

6. Creatine salts of claim 1 wherein $A^{\ominus}$ is the anion of malic acid.

7. A process for the preparation of salts of claims 1-6, comprising:

a) contemporaneous dissolution of creatine and of the organic acid in water;

b) concentration of the solution up to complete crystallization and drying of the obtained product.

8. A process for the preparation of salts of claims 1-6, comprising:

a) reaction of creatine with the organic acid in a water-immiscible solvent at a temperature from the

room temperature to 50°C;

b) filtration and drying of the obtained product.

9. Use of salts of claims 1-6, as additive in dietetic and/or alimentary compositions.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C279/14 A23L1/305

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 84, no. 1, 1976 Columbus, Ohio, US; ZHURAVLEVA I.A. 'GLYCOLYSIS AND SOME REACTIONS OF THE PENTOSEPHOSPHATE PATHWAY IN DDT-SENSITIVE AND -RESISTANT MUSCA DOMESTICA' page 13433; see abstract & MED. PARAZITOL PARAZIT. BOLEZNI, vol. 44, no. 1, 1975 pages 53-58, ---	1
X	WO,A,94 02127 (HULTMAN ERIC ;HARRIS ROGER C (GB)) 3 February 1994 see page 7, line 11 - line 13; claims --- -/--	9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 November 1995	12. 12 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Sánchez García, J.M.

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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E	EP,A,0 669 083 (SUEOKA HARUHIKO) 30 August 1995 see page 4, line 38 - line 49	1,5,9

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/02897

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2140768	03-02-94
		EP-A-	0652748	17-05-95
		FI-A-	950302	24-01-95
		JP-T-	7509230	12-10-95
		NO-A-	950250	23-01-95
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		NO-A-	950719	29-08-95